

### Remarks

The May 6, 2003 Official Action has been carefully reviewed. In view of the amendments submitted herewith and these remarks, favorable reconsideration and allowance of this application are respectfully requested.

At the outset it is noted that a shortened statutory response period of three (3) months was set forth in the May 6, 2003 Official Action. The initial due date for response, therefore, was August 6, 2003. A petition for a 1 month extension of the response period is presented with this response, which is being filed within the one month extension period.

As another preliminary matter, it is noted that the Examiner has withdrawn claims 41 and 42 from further consideration as allegedly pertaining to non-elected inventions. Applicants once again reserve the right to file one or more continuing applications, as provided under 35 U.S.C. §121, on the subject matter of the claims that are withdrawn from consideration by the Examiner in this application.

In the May 6, 2003 Official Action, the specification was objected to in several respects, including an objection based on the stray markings appearing in the chemical structures shown at pages 35, 45, 51, and 56 of the present specification and an objection for incomplete compliance with the sequence listing requirements of 37 C.F.R. §§1.821 to 1.825.

The Examiner also indicates that the drawings are considered informal by the Draftsperson and require correction. Applicants have addressed the concerns of the Draftsperson and submit herewith new copies of the allegedly informal figures.

In addition, the objection to claim 38 under 35 U.S.C. §132 as allegedly introducing new matter into the disclosure has been maintained. It is unclear to Applicants

as to why an objection under 35 U.S.C. §132 is being made by the Examiner when it is noted in the MPEP at §706.03(o) that "35 U.S.C. §132 should be employed as a basis for objection to amendments to the abstract, specification or drawings" but not to claims. However, Applicants have cancelled claim 38 thereby rendering this objection moot and respectfully request the withdrawal of the objection of claim 38 under 35 U.S.C. §132.

Claim 28 has been objected to under 37 C.F.R. §1.75(c) for failing to further limit the subject matter of a previous claim. Applicants have rendered this objection moot by cancelling claim 28.

Turning to the grounds of rejection set forth in the May 6, 2003 Official Action, claims 16-30, 38-40, and 43 stand rejected as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. The Examiner gives her reasons for the rejections in paragraphs 27-36 of the May 6, 2003 Official Action.

Claims 17-30 and 38 are rejected under 35 U.S.C. §112, first paragraph, as the specification allegedly lacks a written description of the subject matter of those claims, such as would reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Claim 16 is rejected under 35 U.S.C. §102(b) as allegedly anticipated by Kuhstoss et al. (Gene (1996) 183:231-36).

Claims 17-25, 28-30, 38-40, and 43 are rejected under 35 U.S.C. §103(a) as allegedly unpatentable over the combined disclosures of U.S. Patent No. 5,712,146 to Khosla et al. and Khosla (Chemical Reviews (1997) 97:2577-2590).

The foregoing objections and rejections constitute all of the grounds set forth in the May 6, 2003 Official Action for refusing the present application.

The specification has been amended to include sequence identifiers for the sequences present in Figures 2A-2D, 4A-4C, and 7 as required by the Examiner to comply with the requirements of 37 C.F.R. §§1.821 to 1.825. Additionally, replacement chemical structures have been provided to replace the ones that contained stray marks generated artificially by the word processor employed. These amendments are believed to overcome the above-noted specification objections and Applicants respectfully request their withdrawal.

The present claim amendments and additions are believed to overcome certain of the objections and rejections set forth in the May 6, 2003 Official Action.

Claim 43 has been amended to refer to a "natural KSq domain" instead of the "Dec" domain comprising both KSq and CLF. Support for this amendment can be found at page 18, lines 12-20. Support for the recitation of the requirement that "at least the first extension module ... is not naturally associated with a loading module that effects decarboxylation" can be found at page 18, lines 5-9. Additionally, support for the sizes of the macrolides can be found at page 20, lines 7-13 and page 21, lines 16-22.

New claims 44-63 are presented with this amendment and their entry is respectfully requested. Claims 16-19, 21, 22, 26-28, and 38-42 have accordingly been cancelled.

New claims 44 and 45 depend from amended claim 43. The claims are directed to 12-membered and 14 membered macrolides, respectively. Support for theses limitations can be found at page 21, lines 16-22.

New claims 46 and 54 are based on amended claim 43. Support for the recitation in claim 46 of the phrase that "the acyltransferase domain is derived from any extension module of a type I polyketide synthase" can be found at page 23, lines 2-7. Claim 54 recites an engineered-KSq domain which "has been genetically engineered to effect decarboxylation of a loaded optionally substituted malonyl by mutating the active

site cysteine residue to a glutamine residue." Support for this recitation can be found at page 18, lines 12-20.

New claims 47-53 and 55-62 correspond to previous claims. The correspondence between these claims is as follows:

<u>New Claim</u>	<u>Previous Claim</u>
47, 58	23
48, 59	24
49, 60	25
50, 61	26
51, 62	27
52	29
53, 63	30
55	20
56	21

Claim 57 also corresponds to claim 22, but has been substantially re-worded because of its change in claim dependency and to eliminate the allegedly ambiguous phrase "N-terminal ketosynthase-like domain" (see hereinbelow). Applicants believe, however, that the spirit of claim 22 is encompassed by new claim 57.

No new matter has been introduced into this application by reason of any of the amendments presented herewith. For the most part, the effect of the foregoing amendments is merely to make express that which was implicit in the application as originally presented.

**CLAIMS 17-30 AND 38 FULLY COMPLY WITH THE REQUIREMENTS OF 35  
U.S.C. §112, FIRST PARAGRAPH**

The Examiner has maintained the rejection of claim 38 and newly rejected claims 17-30 under 35 U.S.C. §112, first paragraph as allegedly introducing new matter for the inclusion of the proviso that the synthase is "not composed of the loading module of the tylosin polyketide synthase coupled to the spiramycin polyketide synthase minus its natural loading module." Applicants maintain that the subject matter in question is described at pages 12-13 and respectfully disagree with the Examiner's requirement that the subject

matter must have been used in a "negation statement." In an effort to advance the prosecution of the instant application, however, Applicants have cancelled claims 17 and 38. The disputed proviso is present only in these two claims while claims 18-30 were dependent on claim 17. Additionally, Applicants point out that the subject matter alleged to be new matter by the Examiner has not been added to any of the new claims. Applicants submit that the rejection of claims 17-30 and 38 under 35 U.S.C. §112, first paragraph has been rendered moot and respectfully request its withdrawal.

**CLAIMS 16-30, 38-40, AND 43, AS AMENDED, AND NEWLY ADDED  
CLAIMS 44-63 MEET THE REQUIREMENTS OF 35 U.S.C. §112, SECOND  
PARAGRAPH**

The Examiner has rejected claim 16 for alleged indefiniteness for failing to positively recite that the polyketide synthase is a type I polyketide synthase and for including the term "substantially." While claim 16 has been cancelled, Applicants have adopted the Examiner's suggestions and positively recited "type I" in all of the added claims. Applicants have also avoided using the allegedly indefinite term "substantially." Therefore, Applicants respectfully request the rejection of claim 16 under 35 U.S.C. §112, second paragraph be withdrawn.

The Examiner asserts that the term "loading module" is indefinite and therefore rejects claims 16-30 and 38. Specifically, the Examiner asserts that "loading module" is unclear because the term as described in claims 39 and 43 contains an ACP domain, but claim 28 allegedly attempts to further limit a loading module by requiring it to include an ACP domain. As noted hereinabove, Applicants have cancelled claim 28. Therefore, any possible ambiguity that may have been engendered by the phrase "loading domain" has been eliminated. Applicants respectfully request the withdrawal of the rejection of claims 16-30 and 38 under 35 U.S.C. §112,

second paragraph.

Claims 19 and 39 were rejected by the Examiner as allegedly being indefinite for reciting the option of having either a CLF domain or a ketosynthase  $\beta$  domain which, the Examiner asserts, are identical. This rejection has been rendered moot by the cancellation of claims 19 and 39 and the fact that none of the newly amended or added claims contain recitation of either a CLF domain or a ketosynthase  $\beta$  domain.

Additionally, the Examiner has rejected claim 22 as the nature of the KSq-ATq is allegedly unclear because of the recitation of the phrase "N-terminal ketosynthase-like domain." Applicants have cancelled claim 22 and none of the newly amended or added claims, specifically claim 57 which corresponds to claim 22, recite this phrase. Therefore, the rejection of claim 22 under 35 U.S.C. §112, second paragraph is moot and should be withdrawn.

Claim 29 has been deemed indefinite by the Examiner for allegedly lacking antecedent basis for the phrase "the KSq domain." Applicants have amended claim 29 to recite that the whole loading module, as opposed to just the KSq domain, is derived from the listed polyketide synthase multienzymes. Support for this amendment can be found at page 20, lines 14-18 and page 22, lines 17-22. Claim 29 has also been amended to depend from claim 43 in which there is antecedent basis for the recitation of "the loading module" as now recited in amended claim 29. Additionally, newly added claim 52, which corresponds to claim 29, recites a loading module, for which there is antecedent basis in claim 46, instead of a "KSq domain." Thus, Applicants submit that these amendments have overcome this rejection and respectfully request it be withdrawn.

The Examiner has rejected claim 30 on the grounds that the metes and bounds of the phrase "variants of rifamycin ..." are unclear. To resolve the perceived indefiniteness, Applicants have amended claim 30 to recite that the

polyketides variants "differ from the natural compound in the incorporation of acetate starter units or propionate starter units." Support for this amendment can be found, for example, at page 21, lines 1-15 and page 22, lines 8-22. The spirit of this amendment has been incorporated into newly added claims 53 and 63 which correspond to claim 30. Applicants submit that the amendment to claim 30 is sufficient to allow a skilled artisan to readily recognize the metes and bounds of the phrase and the scope of the claim, thereby overcoming the rejection.

Claims 38-40 are considered indefinite by the Examiner for the inclusion of the phrases "at least a part of" and "portion thereof." Inasmuch as claims 38-40 have been cancelled, the rejection of claims 38-40 has been rendered moot. Additionally, Applicants have taken care not to use the allegedly unclear phrases in the newly amended and added claims.

Lastly, claims 39, 40, and 43 have been determined to be indefinite by the Examiner for lacking consistency between terms and for using the phrase "engineered domains" in conjunction with the phrase "derived from different sources." Applicants point out to the Examiner that the terms "(dec)" and "(decarboxy)" which were used previously have been eliminated from the current claim set by the cancellation of claims 39 and 40 and by amendment to claim 43. Therefore, the rejection of claims 39, 40, and 43 for lacking consistency between terms has been rendered moot.

With regard to the phrases "engineered domains" and "derived from different sources, Applicants have eliminated the ambiguity perceived by the Examiner by cancelling claims 39 and 40 and removing the allegedly unclear phrases from claim 43 by amendment. Newly added claim 54 does recite an "engineered-KSq domain," but specifically recites that the domain has been "genetically engineered ... by mutating the active site cysteine residue to a glutamine residue." In view

of the recitation, claim 54 can not be considered indefinite for the recitation of an engineered domain, and the rejection of claims 39, 40, and 43 for indefiniteness has been overcome.

In view of all the foregoing, Applicants respectfully request the rejections of claims 16-30, 38-40, and 43 under 35 U.S.C. §112, second paragraph be withdrawn.

**CLAIM 16 AND NEWLY ADDED CLAIMS 44-63 ARE NOT ANTICIPATED BY  
KUHSTOSS ET AL.**

The Examiner has rejected claim 16 as allegedly anticipated by Kuhstoss et al. (Gene (1996) 183:231-236). The Examiner's arguments against claim 16 are essentially the same as those previously advanced in rejecting claims 17, 18, 20-22, 24, and 28-30 in the Official Action dated May 3, 2002. Notably, the rejection of claims 17, 18, 20-22, 24, and 28-30 under 35 U.S.C. §102 was withdrawn by the Examiner in the instant Official Action because of the addition of a proviso to claim 17. The Examiner, however, contends that the added proviso is new matter. As noted hereinabove, the proviso which the Examiner considers to be new matter has been removed from the claims. Furthermore, claims 16 and 17 have been cancelled thereby rendering these rejections moot.

Applicants note, however, that amended claim 43 approximates claims 16 and 17. Applicants have further amended claim 43 to recite that the "polyketide produced is a 12 or 14-membered macrolide." Support for this amendment, as noted hereinabove, can be found at page 20, lines 7-13 and page 21, lines 16-22 wherein the produced polyketides are described as "12-, 14-, or 16-membered macrolides." The present amendment to claim 43 cannot be regarded as involving new matter when considered in light of *In re Johnson*, 194 USPQ 187 (CCPA 1977), which stands for the proposition that an Applicant for patent is permitted to narrow his or her claims to avoid having them read on subject matter which Applicant is not entitled to claim. Furthermore, the disclosure of the



production of a range of 12-, 14-, and 16-membered macrolides, clearly supports a claim limited to 12- or 14-membered macrolides. See, for example, In re Wertheim, 191 USPQ 9 (CCPA 1976) and In re Blaser, 194 USPQ 122 (CCPA 1977). The disclosure of Kuhstoss et al. is clearly limited to the disclosure of a single 16-membered macrolide as indicated by the Examiner (see also Figure 3). Therefore, the claimed invention cannot be considered anticipated by Kuhstoss et al. In view of all of the foregoing, Applicants respectfully request the withdrawal of the rejection of claim 16 under 35 U.S.C. §102.

**CLAIMS 17-25, 28-30, 38-40, AND 43 ARE NOT RENDERED OBVIOUS BY  
U.S. PATENT NO. 5,712,146 IN VIEW OF KHOSLA**

The Examiner has maintained the rejection of claims 19, 23, 25, and 38-40 and newly rejected claims 17, 18, 20-22, 24, 28-30 and 43 as allegedly rendered obvious by U.S. Patent No. 5,712,146 in view of Khosla (Chemical Reviews (1997) 97:2577-2590).

The criterion for determining obviousness under §103 is whether the prior art supplies some motivation or incentive to one of ordinary skill in the art to arrive at the invention as claimed. In re Dow Chemical Company, 5 U.S.P.Q. 2d 1929 (Fed. Cir. 1988). Obviousness cannot be established by combining teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination. In re Fine, 5 U.S.P.Q.2d (Fed. Cir. 1988). Moreover, the teaching or suggestion supporting the desirability or the combination must be found in the prior art, not in applicant's disclosure. In re Fritch, 23 U.S.P.Q.2d 1780 (Fed. Cir. 1992). Under these standards, neither of the cited references, considered singly or in combination, render obvious the invention as claimed in claim 17-25, 28-30, 38-40, and 43 or any of the newly added claims.

The Examiner has asserted that the motivation for

combining the teachings of the two references comes from "the great therapeutic potential of novel polyketides that can be easily produced, in combinatorial fashion, using the system of mixing and matching described [in U.S. Patent 5,712,146]."

Applicants strenuously disagree with the Examiner's assessment of the motivation to combine the two teachings. Specifically, in Khosla at page 2581, left column 1, second full paragraph, Khosla sets forth that the spiramycin loading domain includes "a ketosynthase domain whose active-site cysteine is replaced with a glutamine (and therefore is presumably **inactive**)" [emphasis added]. Additionally, Khosla also attaches no significance to the presence of the KSq domain in the loading module of the spiramycin PKS by referring explicitly to the "loading AT-ACP of the spiramycin PKS (which uses an acetyl primer)." Furthermore, the instant invention demonstrates that the use of an acetyl primer by spiramycin PKS, as indicated in the foregoing quote from Khosla, is incorrect. Applicants submit that the combination of the above teachings actually teaches away from combining the two references. While the motivation for generating polyketide synthases is great because of the great therapeutic potential of the created polyketides, a skilled artisan would clearly not set out to generate hybrid polyketide synthases with loading modules containing KSq domains that are described as "inactive." Therefore, the conclusion is inescapable that no incentive or motivation for the combination of the teachings can be found in the cited prior art.

Applicants also continue to take exception to the Examiner's unfounded extrapolation of type II polyketide synthases to type I polyketide synthases. Specifically, the Examiner asserts that U.S. Patent 5,712,146 "describes hybrid PKS systems" and that Khosla provides a reasonable expectation of success with respect to the combination of genes, modules, domains, and portions of polyketide synthases "due to extensive similarities among modular and aromatic PKS

enzymes." However, in Khosla at page 2579, column 2, end of first full paragraph, modular polyketide synthases are referred to as a "fundamentally new paradigm." Furthermore, Applicants could not find any disclosure in Khosla to support the allegation that "extensive similarities among modular and aromatic PKS enzymes" exist such that the engineering of type II polyketide synthases could be extrapolated to type I polyketide synthases. To the extent the rejection of claims 17-25, 28-30, 38-40, and 43 is based on facts within the personal knowledge of the Examiner, it is respectfully requested that the Examiner make such facts of record in the form of an affidavit, as provided in 37 C.F.R. §1.107(b), so that Applicants may be better apprised of the Examiner's position and take such responsive action as may be appropriate, in accordance with Rule 104(d)(2). Applicants also maintain that U.S. Patent 5,712,146 discloses no practicable way of making products of modular polyketide synthases and, therefore, submit that it does not broadly describe hybrid PKS systems as asserted by the Examiner. Indeed, Khosla also indicates that "the extrapolation of the same approach to study modular PKSs poses several significant conceptual and technical challenges" (Kao et al. (1994) Science 22:509-512; see page 509, right column, first full paragraph). Therefore, Applicants submit that there is no motivation to combine the teachings of U.S. Patent 5,712,146 regarding type II polyketide synthases and Khosla regarding modular polyketide synthases.

In light of the foregoing, Applicants respectfully request the withdrawal of the rejection of claims 17-25, 28-30, 38-40, and 43 under U.S.C. §103.

#### CONCLUSION

In view of the amendments presented herewith and the foregoing remarks, it is respectfully urged that the objections and rejections set forth in the May 6, 2003

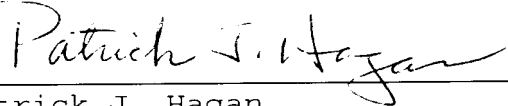
Official Action be withdrawn and that this application be passed to issue.

In the event the Examiner is not persuaded as to the allowability of any claim, and it appears that any outstanding issue may be resolved through a telephone interview, the Examiner is requested to telephone the undersigned attorney at the phone number given below.

Respectfully submitted,

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